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Docket No. 2094/65503-B/JPW/MEB

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Elena Feinstein and Orna Mor

Serial No. : 09/825,682 Examiner: D. Johannsen

Filed : April 4, 2001 Group Art Unit: 1634

For : SEQUENCES CHARACTERISTIC OF BLADDER CANCER

1185 Avenue of the Americas
New York, New York 10036
January 14, 2003

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

INFORMATION DISCLOSURE STATEMENT

To the best of the applicants' knowledge, this Information Disclosure Statement is being submitted before issuance of a first Office Action on the merits under 37 C.F.R. §1.97(b)(3). Therefore, the subject Information Disclosure Statement shall be considered.

In accordance with their duty of disclosure under 37 C.F.R. §1.56 and §1.97(a)-(b) applicants therefore would like to direct the Examiner's attention to the following references, which are listed on Form PTO-1449 (**Exhibit A**). The references are listed below as items 1-18 and copies are attached hereto as **Exhibits 1-18**.

1. United States Patent No. 5,422,243, issued to Jalkanen et al. on June 6, 1995 (**Exhibit 1**);

2. United States Patent No. 5,856,136, issued to Au-Young on January 5, 1999 (**Exhibit 2**);

3. United States Patent No. 6,207,380, issued to Billing-Medel et al. on March 27, 2001 (**Exhibit 3**);

4. United States Patent No. 6,335,170, issued to Orntoft on January 1, 2002 (**Exhibit 4**);

5. United States Patent Application Serial No. 09/670,672, filed September 27, 2000 on behalf of Feinstein and Mor (**Exhibit 5**);

6. PCT International Application No. PCT/US00/41005, filed September 27, 2000, International Publication No. WO 01/22864 A2, published April 5, 2001 (**Exhibit 6**);

7. Ozen, "Bladder Cancer," *Curr. Opin. Oncol.* 10(3):273-278 (1998) (**Exhibit 7**);

8. Torti and Lum, "The Biology and Treatment of Superficial Bladder Cancer," *J. Clin. Oncol.* 2(5):505-531 (1984) (**Exhibit 8**);

9. Grossman, "New Methods for Detection of Bladder Cancer," *Semin. Urol. Oncol.* 16(1):17-22 (1998) (**Exhibit 9**);

10. Sarver et al. "Exploring Catalytic RNAs (Roibozymes) as Anti-HIV Agents," pp. 305-325 in *Gene Regulation and AIDS* by Papas, Portfolio Publishing Co., Woodlands, Texas (1990) (**Exhibit 10**);

11. Lacombe et al., "Overexpression of p53 protein in a high-risk population of patients with superficial bladder cancer before and after bacillus Calmette-Guerin therapy; correlation to clinical outcome," *J. Urol.* 153(3) Part 1:564-572 (1995)(**Exhibit 11**);

12. Herskowitz "Functional inactivation of genes by dominant negative mutations" *Nature* 329: 219-222 (1987)(**Exhibit 12**);

13. Hudson and Herr, "Carcinoma *in situ* of the bladder," *J. Urol.* 153(3) Part 1:564-572 (1995)(**Exhibit 13**);

14. Rosenthal et al., "Human bladder tumour cDNA library derived EST 15", Geneseq032802 Accession No. AAZ24403, submitted February 2000 (**Exhibit 14**);

15. National Institutes of Health, Mammalian Gene Collection, "Homo sapiens cDNA clone", EST Accession No. BG291376, submitted February 2000 (**Exhibit 15**);

16. Quark Biotech Inc., "Bladder cancer-associated sequence, TCC75E3", Geneseq032802 Accession No. AAS01308, submitted July 2001 (**Exhibit 16**);

17. Quark Biotech Inc., "Bladder cancer-associated sequence, TCC94G3", Geneseq032802 Accession No. AAS01297, submitted July 2001 (**Exhibit 17**);

18. Billing-Medel et al., "Sequence 7 from patent US 6207380", GeneEmbl Accession No. AR139477, submitted June 2001 (**Exhibit 18**).

The above listed references 1, 3, 4, 6, and 14-18 were cited in a search report issued in connection with an international counterpart of the subject application. A copy of the search report is attached hereto as **Exhibit B**.

Applicants would like to draw the Examiner's attention to the following item:

19. Culver, "Site-Directed recombinant for repair of mutations in the human ADA gene," (Abstract) *Antisense DNA & RNA based therapeutics*, Coronado, California (1998).

Applicants submit hereto as **Exhibit C** a copy of an email message indicating that this item is no longer available.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Information Disclosure Statement. If any such fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

1/14/03
Date

John P. White
Reg. No. 28,678

Form PTO-1449	U.S. Department of Commerce Patent and Trademark Office	Atty. Docket No. 65503-B	Serial No. 09/825,682
	INFORMATION DISCLOSURE CITATION BY APPLICANT (Use several sheets if necessary)	Applicants Elena Feinstein and Orna Mor	
		Filing Date April 4, 2001	Group 1634

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U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date if Appropriate
		5422243	06/06/95	Jalkanen et al.			
		5856136	01/05/99	Au-Young			
		6207380	03/27/01	Billing-Medel et al.			
		6335170	01/01/02	Orntoft			
		096707	09/27/00	Feinstein and Mor			

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation Yes	Translation No
✓	WO	0122864	04/05/01	PCT				

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

✓		Ozen, "Bladder Cancer," *Curr. Opin. Oncol.* 10(3):273-278 (1998)
✓		Torti and Lum, "The Biology and Treatment of Superficial Bladder Cancer," *J. Clin. Oncol.* 2(5):505-531 (1984)
✓		Grossman, "New Methods for Detection of Bladder Cancer," *Semin. Urol. Oncol.* 16(1):17-22 (1998)
✓		Sarver et al. "Exploring Catalytic RNAs (Roibozymes) as Anti-HIV Agents," pp. 305-325 in *Gene Regulation and AIDS* by Papas, Portfolio Publishing Co. Woodlands, Texas (1990)
✓		Culver, "Site-Directed recombinant for repair of mutations in the human ADA gene," (Abstract) *Antisense DNA & RNA based therapeutics*, Coronado, California (1998)
✓		Lacombe et al., "Overexpression of p53 protein in a high-risk population of patients with superficial bladder cancer before and after bacillus Calmette-Guerin therapy; correlation to clinical outcome," *J. Urol.* 153(3) Part 1:564-572 (1995)
✓		Herskowitz "Functional inactivation of genes by dominant negative mutations" *Nature* 329: 219-222 (1987)
✓		Hudson and Herr, "Carcinoma *in situ* of the bladder," *J. Urol.* 153(3) Part 1:564-572 (1995)

EXAMINER	DATE CONSIDERED

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO-1449	U.S. Department of Commerce Patent and Trademark Office	Atty. Docket No. 65503-B	Serial No. 09/825,6[illegible]
		Applicants Elena Feinstein and Orna Mor	
	INFORMATION DISCLOSURE CITATION BY APPLICANT (Use several sheets if necessary)	Filing Date April 4, 2001	Group 1634

OIPE JC10 JAN 21 2003 PATENT TRADEMARK

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OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

		Rosenthal et al., "Human bladder tumour cDNA library derived EST 15", Geneseq032802 Accession No. AAZ24403, submitted February 2000
		National Institutes of Health, Mammalian Gene Collection, "Homo sapiens cDNA clone", EST Accession No. BG291376, submitted February 2000
		Quark Biotech Inc., "Bladder cancer-associated sequence, TCC75E3", Geneseq032802 Accession No. AAS01308, submitted July 2001
		Quark Biotech Inc., "Bladder cancer-associated sequence, TCC94G3", Geneseq032802 Accession No. AAS01297, submitted July 2001
		Billing-Medel et al., "Sequence 7 from patent US 6207380", GeneEmbl Accession No. AR139477, submitted June 2001

EXAMINER	DATE CONSIDERED

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

JPW

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
JOHN P. WHITE
COOPER & DUNHAM LLP
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

JAN - 6 2003

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

	Date of Mailing (*day/month/year*) 31 DEC 2002
Applicant's or agent's file reference 65503-B-PCT	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US02/12774	International filing date (*day/month/year*) 04 April 2002 (04.04.2002)
Applicant QUARK BIOTECH, INC.	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report. Article 19: 2/28/2003 SMC

Where? Directly to the International Bureau of WIPO, 34, chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35 IDS: 3/31/2003 (65503-A, 65503-B)

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90 *bis*.1 and 90 *bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices. Filed 10/29/02 SMC 12/4/02 SMC 10/4/2003 SMC

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Commissioner for Patents Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Valerie Bell-Harris for Diana B. Johannsen Telephone No. 703/308-0196

Form PCT/ISA/220 (April 2002) (*See notes on accompanying sheet*)

Applicants: Elena Feinstein and Orna Mor
U.S. Serial No.:09/825,682
Filed: April 4, 2001
Title: SEQUENCES CHARACTERISTIC OF BLADDER CANCER
Exhibit B

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 65503-B-PCT/	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US02/12774	International filing date (*day/month/year*) 04 April 2002 (04.04.2002)	(Earliest) Priority Date (*day/month/year*) 04 April 2001 (04.04.2001)
Applicant QUARK BIOTECH, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the Report**
   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
   ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:
   ☒ contained in the international application in written form.
   ☒ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
2. ☐ **Certain claims were found unsearchable** (See Box I).
3. ☒ **Unity of invention is lacking** (See Box II).
4. With regard to the **title**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. ____
   ☐ as suggested by the applicant. ☐ None of the figures
   ☐ because the applicant failed to suggest a figure.
   ☐ because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/12774

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: Please See Continuation Sheet

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/12774

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12Q 1/68; G01N 33/53; C12P 19/34; C07H 21/04
US CL : 435/6, 7.1, 91.2, 91.51; 536/23.5

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/6, 7.1, 91.2, 91.51; 536/23.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,207,380 B1 (BILLING-MEDEL et al) 27 March 2001 (27.03.2001), see entire reference, especially column 4, line 28-column 6, line 34, Figure 1, Examples 1 and 9).	1-2, 4-6
A,P	GenEmbl Accession No. AR139477, BILLING-MEDEL et al "Sequence 7 from patent US 6207380," June 2001.	1-2, 4-6
X	Geneseq032802 Accession No. AAZ24403, ROSENTHAL et al "Human bladder tumour cDNA library derived EST 15," February 2000.	1-3
--- Y		4-6
X	EST Accession No. BG291376, NIH-MGC "Homo sapiens cDNA clone," February 2002.	1-3
--- Y		4-6
X,P	WO 01/22864 A2 (QUARK BIOTECH, INC.) 05 April 2001 (05.04.2001), see entire reference, especially Table 3.	1-9, 24
A,P	Geneseq032802 Accession No. AAS01308, QUARK BIOTECH INC. "Bladder cancer-associated sequence, TCC75E3," July 2001.	1-9, 24
A,P	Geneseq032802 Accession No. AAS01297, QUARK BIOTECH INC. "Bladder cancer-associated sequence, TCC94G3," July 2001.	1-9, 24

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
07 November 2002 (07.11.2002)

Date of mailing of the international search report
31 DEC 2002

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703)305-3230

Authorized officer
Valerie Bell-Harris for
Diana B. Johannsen

Telephone No. 703/308-0196

Form PCT/ISA/210 (second sheet) (July 1998)

PCT/US02/12774

INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	US 6,335,170 B1 (ORNTOFT) 01 January 2002 (01.01.2002), see entire reference.	1-9, 24
A	US 5,422,243 A (JALKANEN et al) 06 June 1995 (06.06.1995), see entire reference.	1-9, 24

INTERNATIONAL SEARCH REPORT

PCT/US02/12774

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions that are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-9 and 24, drawn to methods of diagnosing bladder cancer in which nucleic acids are detected. Group I limited to the first polynucleotide listed in Table 3, the first mentioned invention, is the invention that will be searched in accordance with PCT Article 17(3)(a). Additional Groups may be elected.

Group II, claims 1-9, 18-19 and 24-25, drawn to methods of diagnosing bladder cancer in which polypeptides are detected.

Group III, claims 10-13 and 22-23, drawn to polynucleotides.

Group IV, claims 14-16, drawn to polypeptides.

Group V, claim 17, drawn to antibodies.

Group VI, claim 20, drawn to methods of treating bladder cancer by administering a compound that inhibits a gene.

Group VII, claim 20, drawn to methods of treating bladder cancer by administering a compound that inhibits a polypeptide.

Group VIII, claim 21, drawn to a gene therapy vehicle.

The inventions listed as Groups I-VIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons.

As provided in Annex B Rule 13.2 Circumstances in Which the Requirement of Unity of Invention Is to Be Considered Fulfilled - Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

The first claimed invention, Group I, is drawn to methods of diagnosing bladder cancer in which nucleic acids are detected. Billing-Medel et al (US Patent No. 6,207,380 B1 [3/2001]) disclose methods of diagnosing bladder cancer in which a polynucleotide meeting the limitations of the instant claims is detected (e.g., a polynucleotide "at least 70% homologous" to instant SEQ ID NO: 1) (see Figure 1; col 5, line 6-col 6, line 34; Examples 1, 9; alignment of SEQ ID NO: 1 with SEQ ID NO: 7 of Billing-Medel et al). Accordingly, the nucleic acids encompassed by Group I cannot constitute a shared special technical feature as defined by PCT Rule 13.2. Further, Groups I-VIII do not share any other property that could constitute a special technical feature within the meaning of PCT Rule 13.2. Groups III, IV, V and VIII are drawn to molecules having different structures and functions. The nucleic acids of Group III are composed of nucleotides linked by phosphodiester bonds and function in, e.g., methods of hybridization. The gene therapy vehicle of Group VIII is also composed of nucleotides. However, the vehicle requires a particular structure and structural elements that allow it to be used in gene therapy, and functions in treatment of patients. Accordingly, both the structural and functional requirements of the inventions of Groups III and VIII differ. The proteins and antibodies of Group IV and V are each composed of amino acids linked by peptide bonds. However, the molecules have different functional properties and structural requirements. Particularly, the antibodies of Group V are glycosylated, have a particular tertiary structure, and have particular binding properties that render them distinct from other proteins. The methods of Groups I, II, VI and VII employ different sets of reagents in different process steps. The method of Group I requires the use of, e.g., nucleic acids probes or oligonucleotide primers in steps of hybridization and/or amplification to achieve the objective of diagnosis. Group II requires the use of, e.g., antibodies in steps of specifically binding proteins to achieve the objective of diagnosis. Group VI requires administration of, e.g., an antisense nucleic acid to a subject to achieve the objective of treatment. Group VII requires administration of, e.g., an antibody to a subject to achieve the objective of treatment. Thus, Groups I, II, VI and VII do not share common objectives, effects and/or steps, such that these features of the invention might constitute a shared special technical feature.

INTERNATIONAL SEARCH REPORT

Situations in which a single claim defines alternatives (chemical or non-chemical) are also governed by Rule 13.2 (MPEP Administrative Instructions, Annex B, "Markush practice"). In this special situation, the requirement of a technical interrelationship and the same or corresponding special technical features as defined in Rule 13.2, shall be considered to be met when the alternatives are of a similar nature:

(i) When the Markush grouping is for alternatives of chemical compounds, they shall be regarded as being of a similar nature where the following criteria are fulfilled:

(A) all alternatives have a common property or activity, and

(B)(1) a common structure is present, i.e., a significant structural element is shared by all of the alternatives, or

(B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.

Groups I-VIII have been presented in an improper Markush format, as the claims encompass the use of multiple polynucleotides and polypeptides that are not "of a similar nature." The numerous polynucleotides encompassed by the claims, as well as the polypeptides encoded thereby, and the antibodies that bind those polypeptides, have different structures, and are not disclosed as having a common property or activity. A reference against one molecule would not be a reference against another. Accordingly, the numerous different molecules encompassed by each of the Groups do not share a special technical feature, and unity of invention is therefore lacking. **Accordingly, if applicant wishes to elect additional Groups (other than Group I limited to the first polynucleotide of Table 3), for each group applicant must elect both a Group and a** SEQ ID NO, or, if applicable, a pair or group of SEQ ID NOS encoding a single polypeptide sequence. Each sequence/pair will constitute a separate subgroup for which the required fees must be paid.

It is also noted that some of applicants claims are written so as to be limited to only a subset of the SEQ ID Nos encompassed by the Groups as a whole (e.g., claim 3 is limited to sequences set forth in Table 6, claim 8 to sequences encoding keratin 13, claims 12-13 to sequences set forth in Tables 4 and 6). These claims will be examined only to the extent that they read upon the elected SEQ ID NO or SEQ ID Nos.

With respect to Groups I-II and VI-VII, it is noted that in claims 1-9, 20, and 24, methods of detecting nucleic acids and polypeptides and methods of treating employing nucleic acids and polypeptides are improperly joined. As discussed above, polynucleotides and polypeptides have different structures and different functions. The different products do not share a common property or activity, lack a common structure, and do not belong to a recognized class of chemical compounds. The steps and reagents required to detect nucleic acids differ from the steps and reagents required to detect polypeptides. Similarly, treatment to achieve modulation of nucleic acid expression would require different steps and reagents than treatment to achieve modulation of polypeptide activity. Accordingly, claims 1-9 and 24 have been included in both Group I and Group II, and if either of these groups is elected, will be examined only to the extent those claims read on the elected group. Claim 20 has been included in both Group VI and Group VII, and if either of these groups is elected, will be examined only to the extent the claim reads on the elected group.

Continuation of Box II Item 3:

1-9 and 24, limited to the first polynucleotide of Table 3 and the first 5 polynucleotides of Table 5

Continuation of B. FIELDS SEARCHED Item 3:

USPT, DWPI, Medline Cancerlit, Lifesci, Embase, Biosis, CAPlus, Scisearch, GenEmbl, Geneseq032802, EST, Issued

search terms: bladder, cancer, tumor, tumour, malignan####, carcinoma, hepatocyte growth factor activator inhibitor 2, bikunin, alpha1 microglobulin, syndecan, sdc1, cd138, keratin 13, tissue factor pathway inhibitor 3, tfpi 3; inventors' names; SEQ ID NOS 1, 41-42, 45, 56-57, 62

CHAPTER I
PCT TELEPHONE MEMORANDUM
FOR
LACK OF UNITY OF INVENTION

PCT No.: PCT/US02/12774

Examiner: Diana B. Johannsen

Attorney spoken to: John White/Flynn Barrison

Date of call: 10 October 2002

☒ Amount of payment approved: $1050.00

☒ Deposit account number to be charged: 03-3125

☐ Attorney elected to pay for ALL additional inventions

☒ Attorney elected to pay only for the additional inventions covered by

☒ Group(s): 1; 5 additional subgroups of Group 1 were elected

-- encompassing –

☒ Claim(s): 1-9 and 24, limited to the first 5 polynucleotides of Table 5

☐ Attorney elected NOT to pay for any additional inventions, therefore, only the first claimed invention (Group I) covered by Claim(s) _____ has been searched.

☒ Attorney was orally advised that there is no right to protest for any group not paid for.

☒ Attorney was orally advised that any protest must be filed no later than 15 days from the mailing of the Search Report (PCT/ISA/210).

Time Limit For Filing A Protest

Applicant is hereby given 15 days from the mailing date of this Search Report in which to file a protest of the holding of lack of unity of invention. In accordance with PCT Rule 40.2, applicant may protest the holding of lack of unity only with respect to the group(s) paid for.

Detailed Reasons For Holding Lack of Unity of Invention:
Please See Continuation Sheet

Note: A copy of this form must be attached to the Search Report.

ATTACHMENT TO CHAPTER I PCT TELEPHONE MEMORANDUM FOR LACK OF UNITY OF INVENTION

Continuation of Detailed Reasons For Holding Lack of Unity of Invention:

This application contains the following inventions or groups of inventions that are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-9 and 24, drawn to methods of diagnosing bladder cancer in which nucleic acids are detected. Group I limited to the first polynucleotide listed in Table 3, the first mentioned invention, is the invention that will be searched in accordance with PCT Article 17(3)(a). Additional Groups may be elected.

Group II, claims 1-9, 18-19 and 24-25, drawn to methods of diagnosing bladder cancer in which polypeptides are detected.

Group III, claims 10-13 and 22-23, drawn to polynucleotides.

Group IV, claims 14-16, drawn to polypeptides.

Group V, claim 17, drawn to antibodies.

Group VI, claim 20, drawn to methods of treating bladder cancer by administering a compound that inhibits a gene.

Group VII, claim 20, drawn to methods of treating bladder cancer by administering a compound that inhibits a polypeptide.

Group VIII, claim 21, drawn to a gene therapy vehicle.

The inventions listed as Groups I-VIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons.

As provided in Annex B Rule 13.2 Circumstances in Which the Requirement of Unity of Invention Is to Be Considered Fulfilled -Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

The first claimed invention, Group I, is drawn to methods of diagnosing bladder cancer in which nucleic acids are detected. Billing-Medel et al (US Patent No. 6,207,380 B1 [3/2001]) disclose methods of diagnosing bladder cancer in which a polynucleotide meeting the limitations of the instant claims is detected (e.g., a polynucleotide "at least 70% homologous" to instant SEQ ID NO: 1) (see Figure 1; col 5, line 6-col 6, line 34; Examples 1, 9; alignment of SEQ ID NO: 1 with SEQ ID NO: 7 of Billing-Medel et al). Accordingly, the nucleic acids encompassed by Group I cannot constitute a shared special technical feature as defined by PCT Rule 13.2. Further, Groups I-VIII do not share any other property that could constitute a special technical feature within the meaning of PCT Rule 13.2. Groups III, IV, V and VIII are drawn to molecules having different structures and functions. The nucleic acids of Group III are composed of nucleotides linked by phosphodiester bonds and function in, e.g., methods of hybridization. The gene therapy vehicle of Group VIII is also composed of nucleotides. However, the vehicle requires a particular structure and structural elements that allow it to be used in gene therapy, and functions in treatment of patients. Accordingly, both the structural and functional requirements of the inventions of Groups III and VIII differ. The proteins and antibodies of Group IV and V are each composed of amino acids linked by peptide bonds. However, the molecules have different functional properties and structural requirements. Particularly, the antibodies of Group V are glycosylated, have a particular tertiary structure, and have particular binding properties that render them distinct from other proteins. The methods of Groups I, II, VI and VII employ different sets of reagents in different

process steps. The method of Group I requires the use of, e.g., nucleic acids probes or oligonucleotide primers in steps of hybridization and/or amplification to achieve the objective of diagnosis. Group II requires the use of, e.g., antibodies in steps of specifically binding proteins to achieve the objective of diagnosis. Group VI requires administration of, e.g., an antisense nucleic acid to a subject to achieve the objective of treatment. Group VII requires administration of, e.g., an antibody to a subject to achieve the objective of treatment. Thus, Groups I, II, VI and VII do not share common objectives, effects and/or steps, such that these features of the invention might constitute a shared special technical feature.

Situations in which a single claim defines alternatives (chemical or non-chemical) are also governed by Rule 13.2 (MPEP Administrative Instructions, Annex B, "Markush practice"). In this special situation, the requirement of a technical interrelationship and the same or corresponding special technical features as defined in Rule 13.2, shall be considered to be met when the alternatives are of a similar nature:

(i) When the Markush grouping is for alternatives of chemical compounds, they shall be regarded as being of a similar nature where the following criteria are fulfilled:

(A) all alternatives have a common property or activity, and

(B)(1) a common structure is present, i.e., a significant structural element is shared by all of the alternatives, or (B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.

Groups I-VIII have been presented in an improper Markush format, as the claims encompass the use of multiple polynucleotides and polypeptides that are not "of a similar nature." The numerous polynucleotides encompassed by the claims, as well as the polypeptides encoded thereby, and the antibodies that bind those polypeptides, have different structures, and are not disclosed as having a common property or activity. A reference against one molecule would not be a reference against another. Accordingly, the numerous different molecules encompassed by each of the Groups do not share a special technical feature, and unity of invention is therefore lacking. **Accordingly, if applicant wishes to elect additional Groups (other than Group I limited to the first polynucleotide of Table 3), for each group applicant must elect both a Group and a** SEQ ID NO, or, if applicable, a pair or group of SEQ ID NOS encoding a single polypeptide sequence. Each sequence/pair will constitute a separate subgroup for which the required fees must be paid.

It is also noted that some of applicants claims are written so as to be limited to only a subset of the SEQ ID Nos encompassed by the Groups as a whole (e.g., claim 3 is limited to sequences set forth in Table 6, claim 8 to sequences encoding keratin 13, claims 12-13 to sequences set forth in Tables 4 and 6). These claims will be examined only to the extent that they read upon the elected SEQ ID NO or SEQ ID Nos.

With respect to Groups I-II and VI-VII, it is noted that in claims 1-9, 20, and 24, methods of detecting nucleic acids and polypeptides and methods of treating employing nucleic acids and polypeptides are improperly joined. As discussed above, polynucleotides and polypeptides have different structures and different functions. The different products do not share a common property or activity, lack a common structure, and do not belong to a recognized class of chemical compounds. The steps and reagents required to detect nucleic acids differ from the steps and reagents required to detect polypeptides. Similarly, treatment to achieve modulation of nucleic acid expression would require different steps and reagents than treatment to achieve modulation of polypeptide activity. Accordingly, claims 1-9 and 24 have been included in both Group I and Group II, and if either of these groups is elected, will be examined only to the extent those claims read on the elected group. Claim 20 has been included in both Group VI and Group VII, and if either of these groups is elected, will be examined only to the extent the claim reads on the elected group.

NTACT - IBC USA Customer Services Dept

for Sylvia

Subject: RE: CONTACT - IBC USA Customer Services Dept
Date: Thu, 12 Jul 2001 11:24:25 -0400
From: "Schneider, Marcia" <mschneider@ibcusa.com>
To: "'atoz@actcom.co.il'" <atoz@actcom.co.il>

Ms. Zeitak, We regret that this item is not longer available. Regards, Marcia Schneider

-----Original Message-----
From: atoz@actcom.co.il [mailto:atoz@actcom.co.il]
Sent: Thursday, July 12, 2001 4:36 AM
To: custserv@ibcusa.com; taskm@ibcusa.com
Subject: CONTACT - IBC USA Customer Services Dept

CONTACT - IBC USA Customer Services Dept

Sender's details ¬
Ms Gloria Zeitak
Occupation: Manager
Department:
Name of company: Infomayda
Phone: 97289416044
Fax: 97289411353
e-Mail: atoz@actcom.co.il

* Please send further information by email *

Gloria 's company address ¬
Infomayda
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Kiryat Ekron

70500
ISRAEL (IL)

Nature of business: Information retrieval

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